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Risk factors for incident atrial fibrillation with and without left atrial enlargement in women

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Abstract

Background—Left atrial (LA) enlargement facilitates induction and/or maintenance of atrial fibrillation (AF). However, little is known about risk factors for AF with normal LA size.

Methods—We prospectively followed 34713 initially healthy women for incident AF. Information on echocardiographic LA size at first AF diagnosis was abstracted from medical charts during AF confirmation. LA enlargement was defined as LA diameter >40mm. Using a competing risk approach, we constructed Cox proportional-hazards models to calculate hazard ratios (HR) and 95% confidence intervals (CI) of risk factors for incident AF with and without LA enlargement, respectively.

Results—Among 796 women with incident AF and available LA size, 328 (41%) had LA enlargement. In multivariable competing risk models, the relationship between age and incident AF was stronger in those with (HR 1.12, 95% CI 1.10–1.14) versus without (HR 1.08, 95% CI 1.06–1.09) LA enlargement (p for difference <0.0001). Body weight was associated with AF only in the presence of LA enlargement (HR per 10kg 1.34, 95% CI 1.26–1.43; versus 1.07, 95% CI 0.998–1.14, p for difference<0.0001). Hypertension and height were significantly associated with AF both in the presence (HR 1.99, 95% CI 1.49–2.65; and HR per 10cm 1.36, 95% CI 1.13–1.63) and absence (1.55, 1.25–1.92 and 1.29, 1.10–1.50) of LA enlargement (p for difference 0.17 and 0.66, respectively).

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Conclusions—These data suggest that LA enlargement explains much of the increased AF risk associated with obesity and age. In contrast, height and hypertension appear to also influence AF risk through other mechanisms besides LA enlargement.

Keywords

Atrial fibrillation; left atrium; women; obesity; hypertension

Introduction

The left atrium (LA) plays a key role in the pathogenesis of atrial fibrillation (AF) for at least two reasons. First, most important risk factors for AF occurrence, including age, hypertension and elevated body size, have been identified as major determinants of LA size in the population (1–6). Second, LA enlargement is a consistent and independent risk factor of incident AF in the general population (7, 8). For example in the Cardiovascular Health Study, a 10-mm increment of the anteroposterior LA diameter was associated with a 74% increased risk (95% confidence interval (CI) 44%–111%) of new-onset AF after multivariable adjustment (7). In the Framingham Heart Study, the strong relationship between obesity and AF was completely attenuated after adjustment for LA diameter, suggesting that LA size is an important mediator of this association (6). Therefore, LA enlargement may mediate, at least in part, many of the associations between traditional risk factors and AF.

However, not all individuals with new-onset AF have LA enlargement, and the contribution of traditional AF risk factors in the context of incident AF with normal LA size is unclear. It is also relatively unknown whether the magnitude of the associations between risk factors and incident AF differs in the presence or absence of LA enlargement. These data would be important in order to improve our understanding on how risk factors may induce AF in the population. We therefore evaluated risk factor associations with AF occurring in the setting of normal LA size and assessed differences in AF risk factor associations according to the presence or absence of LA enlargement.

Methods

Study Participants

Study subjects were participants of the Women's Health Study, a completed randomized trial among 39876 women assessing benefits and risks of low-dose aspirin (100 mg every other day) and vitamin E (600 IU every other day) in the primary prevention of cardiovascular disease and cancer in a randomized, double-blind, placebo-controlled trial. Details about the study design have been published previously (9, 10).

Women's Health Study participants are female health professionals in the United States, aged 45 years or older and free of cardiovascular disease, cancer or other major illnesses at study entry. Blinded study treatment ended on March 2nd, 2004. Subsequently, all women were invited to participate in continued observational follow-up, which for the present study was truncated on March 2nd, 2011. For the current analysis, we excluded 897 women with a baseline history of AF and 54 women with a confirmed cardiovascular event (stroke, heart failure or myocardial infarction) prior to study entry. Seven women with significant mitral stenosis at the time of first AF diagnosis were also excluded from this analysis, as mechanisms for AF occurrence probably differ in this subset. Finally, 4205 women who did not participate in the observational follow-up were excluded because their AF could not be reliably confirmed, leaving 34713 participants for the current analysis. The study was approved by the institutional review board of Brigham and Women's Hospital, Boston, and

was monitored by an external data and safety monitoring board. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology (11).

Study variables

Mailed questionnaires at baseline, six months, 12 months and yearly thereafter were used to collect information on baseline characteristics, changes in covariates, study outcomes and other information. Covariates of interest for this study included age, hypertension, height, body weight, diabetes, hypercholesterolemia, smoking, alcohol consumption, physical exercise and self-reported race/ethnicity.

Ascertainment of incident atrial brillation

All study participants were asked about a history of AF at baseline. Incident AF events were ascertained by questionnaire at 48 months and annually thereafter. AF confirmation has been described in detail previously (3, 12). Briefly, all women who participated in continued observational follow-up and indicated an incident AF event on at least one yearly questionnaire were sent a supplemental questionnaire to collect additional information and to obtain written informed consent for medical record review. For all deceased participants who reported an AF episode prior to death, family members were contacted to obtain consent and additional relevant information. An AF event was confirmed by an endpoint committee of cardiovascular physicians if there was electrocardiographic evidence of AF or if the medical records clearly indicated a personal history of AF. Only confirmed AF events were included in this analysis. Paroxysmal AF was defined as self-terminating AF lasting <7 days that did not require cardioversion, as previously described (13).

Ascertainment of LA size

Original reports of echocardiographic studies as close to the first AF diagnosis as possible were abstracted from patient charts by the AF endpoint committee. We defined LA enlargement as an anteroposterior LA diameter >40mm on M-Mode or 2-D echocardiography. If quantitative measures of LA diameter were not available, women were also classified as having LA enlargement if a qualitative description of LA enlargement was provided in the report.

Statistical analysis

Baseline characteristics across groups of women were compared using Kruskal-Wallis tests for continuous variables and chi-square tests for categorical variables. Person-years of follow-up were calculated from the date of return of the baseline questionnaire to the first occurrence of death, new-onset AF, loss to follow-up or March 2nd 2011.

We used an extension of the Cox proportional-hazards model (competing risks model) to calculate hazard ratios (HRs) and 95% CIs for incident AF with and without LA enlargement and to adjust for potential confounders (14). Age-adjusted models were additionally adjusted for height, weight, hypertension, diabetes, highest education level, smoking, physical exercise, alcohol consumption and self-reported race/ethnicity. All covariates were entered in the models as time-varying covariates and updated whenever possible. Women with incident AF and missing data on LA dimensions were censored at the time of AF diagnosis in all models.

Competing risks models allow individual covariates to have different relative risk estimates for incident AF with LA enlargement and incident AF without LA enlargement in a single multivariable model (14). Specifically, stratification on event type as described by Lunn and McNeil (15) allows for estimation of separate associations of each risk factor with the

relative hazard of each outcome under a proportional hazards assumption. This approach can be readily implemented using data augmentation, which requires that each subject has a separate observation for each outcome. The results of this model are identical to those obtained from two separate models for incident AF with and without LA enlargement, where a woman is censored for evaluation of one endpoint when she develops the other.

To evaluate differences for AF risk factors according to LA size, we first compared the full competing risk model to a standard constrained model assuming identical risk factor associations using a likelihood ratio test. In order to test whether risk estimates for each individual risk factor differ according to the two outcomes, we then fit a series of reduced models in which one risk factor at a time was forced to have a single effect estimate across both outcomes, while the effects of all other risk factors were allowed to be different. We again used likelihood ratio tests to compare the full model with the individual reduced models.

Some important variables such as symptom status, AF pattern and time between AF diagnosis and echocardiography are available only in AF cases. We therefore constructed a series of case-only logistic regression models among the 796 women with incident AF and available information on LA size, to additionally adjust for symptom status at AF onset, AF pattern (paroxysmal versus non-paroxysmal), and time between AF diagnosis and echocardiography (16). LA size at AF diagnosis (enlarged versus normal) was the outcome variable in these models and women with normal LA size constituted the reference group. Covariate information as close to AF onset as possible was used for these analyses. Finally, an association between clinical variables and time to echocardiography may confound our findings. We therefore constructed a multivariable logistic regression model with time to echocardiography >1 month as the outcome variable and the same covariates listed above.

Categorical variables were entered in the Cox models using binary indicator variables. All analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina). We considered a two-tailed p value <0.05 to indicate statistical significance.

Results

During a median follow-up of 16.4 (interquartile range 15.6–16.8) years, 1072 confirmed AF events occurred, corresponding to an incidence of 2 events per 1000 person-years of follow-up. Echocardiography studies could be obtained in 817 (76.2%) women with new-onset AF, while information on LA size around AF diagnosis was available in 796 (74.3%). There were no statistically significant differences in baseline characteristics among AF women with and without available information on LA dimensions, as shown in Table 1.

Baseline characteristics

Baseline characteristics of study participants according to LA size are shown in Table 2. LA enlargement was found in 328 (41.2%) of these women, while 468 (58.8%) had normal LA size. Echocardiography was performed later than 1 month after AF onset in 41 (8.8%) women with incident AF and normal LA size, and in 52 (15.9%) women with incident AF and LA enlargement (p for difference 0.002). Overall, 74.8% of all echo studies were performed within 3 months of first AF occurrence. Compared to women with AF in the context of normal LA size, those with LA enlargement were significantly older, taller and heavier. They also had a higher prevalence of hypertension and diabetes mellitus. Women with normal LA size had a significantly higher prevalence of paroxysmal AF as the presenting AF pattern (346 (73.9%) versus 149 (45.4%), p<0.0001), and they were more likely to have AF-related symptoms as compared to those with LA enlargement (91.2% versus 84.2%, p for difference = 0.002).

Competing risk analysis

Results from Cox proportional-hazards models are presented in Table 3. A competing risk model allowing for individual risk factor associations with each AF type provided a better fit than a traditional Cox model constrained to have equal effects on each AF type (χ^2 63.42, 11df, p<0.0001), suggesting differing risk associations for AF with and without LA enlargement for at least some covariates. Specifically, we found that age strongly correlated with incident AF with LA enlargement but remained significantly associated with incident AF without LA enlargement as well (p for difference <0.0001) (Table 3). Body weight and white race/ethnicity were related to incident AF only in the presence of LA enlargement, but the difference in relative risk estimates was significant only for body weight (p <0.0001 for body weight, p=0.12 for race/ethnicity).

As shown in Table 3, hypertension and height were strongly related to incident AF both in the presence and absence of LA enlargement, and the risk estimates were similar for both associations (p for difference 0.17 and 0.66, respectively). Exercise was associated with incident AF without LA enlargement. However, the difference between exercise with and without LA enlargement did not reach statistical significance in the competing risk model (p=0.20). Finally, type 2 diabetes mellitus and smoking were not associated with incident AF in either group of women.

Case-only logistic regression

Similar variables were found to have stronger relationships for AF with LA enlargement as compared to AF without LA enlargement in case-only logistic regression models, as shown in Table 4. Compared to women with AF and normal LA size, the multivariable adjusted risks associated with age (odds ratio (OR) per year 1.05, 95% CI 1.03–1.07) and body weight (OR per 10 kg 1.33, 95% CI 1.20–1.48) were significantly greater among women with incident AF and LA enlargement. These differential relationships were only minimally affected and remained significantly different after additional adjustment for symptom status, AF pattern, and time between AF diagnosis and echocardiography (OR for age 1.04, 95% CI 1.02–1.06, OR for body weight 1.33, 95% CI 1.19–1.48). When our analyses were limited to the 543 women who had their echo performed within 1 month of AF onset, similar findings were again obtained for age (OR 1.05, 95% CI 1.02–1.08) and body weight (OR 1.37, 95% CI 1.20–1.57). None of the clinical covariates, in particular age and body weight, were associated with echocardiography outside the 1 month window around AF diagnosis (data not shown).

Discussion

In this large, prospective study of initially healthy women, we found that several AF risk factors had differential associations for incident AF in the presence or absence of LA enlargement at the time of first AF occurrence. Stronger relative risk estimates for incident AF with LA enlargement compared with normal LA size were found for age, body weight and race/ethnicity, although for the latter the p value for difference was not statistically significant. These data suggest that LA enlargement may mediate the association between these risk factors and incident AF (7, 8).

On the other hand, several AF risk factors, namely age, hypertension, height and exercise were also associated with incident AF in the context of normal LA size, and with regard to height and hypertension, the strength of the association did not differ to that for AF with LA enlargement. While the current study is unable to define underlying mechanisms, our findings nevertheless suggest that the relationships of age, hypertension, height, and exercise

with AF occurrence may be in part explained by mechanisms that do not require LA enlargement.

Both hypertension and new-onset AF have been associated with vascular stiffness and inflammation (17–19), such that these factors may at least in part explain the risk associated with hypertension in AF with normal LA size. Hypertension may also induce LA fibrosis without LA enlargement, subsequently leading to AF in the context of normal LA size (20). With regard to height, it has been hypothesized that the increased risk of AF among taller individuals (4–6) is mainly due to the close relationship between body size and LA size (4). However, we found a strong and significant relationship between adult height and new-onset AF also in women with normal LA size and this risk estimate did not differ from that for AF with LA enlargement. These data may suggest that other factors could also explain why taller individuals have an increased risk of AF, including genetic and/or early life determinants (21). Alternatively, clinically accepted measures for LA size, such as anteroposterior diameter, may be an insensitive tool to quantify LA enlargement in tall individuals. Studies using LA volume instead of diameter are needed to test this hypothesis.

By contrast, the strong relationship of body weight and obesity with new-onset AF described in this and prior studies (4–6) was limited to women who had AF in the presence of LA enlargement. The effect of body weight was not statistically significant among women who had new-onset AF with normal LA size, leading to a highly significant difference in the competing risk model. These data are consistent with at least one prior study, where the increased risk associated with obesity was fully attenuated after adjustment for LA size on echocardiography (6). Future studies are needed in order to assess whether hemodynamic effects, inflammation or other factors lead to LA enlargement and subsequent AF in obese individuals.

The significant relationship between white race/ethnicity and incident AF has been described previously (22). Interestingly, our data suggest that this increased risk may be largely restricted to AF with LA enlargement. The non-significant p value for difference in our competing risk models is probably due to the limited number of non-white women in our sample. It has been shown that Blacks have smaller LA dimensions than Whites even after multivariable adjustment (23, 24), suggesting that Blacks may be less prone to structural LA remodeling and this could underlie part of the relative protection against AF associated with black race (22, 24). Future studies are needed to further investigate this intriguing possibility.

Strengths and limitations

Important strengths of this study include its large sample size, updated AF risk factor information, and medical record confirmation of all incident AF events. Our study also has potential limitations. First, the Women's Health Study participants are initially healthy, middle-aged female health professionals and generalization of our results to other populations should be done cautiously. Second, screening electrocardiograms are not systematically available in this cohort and some asymptomatic cases of AF may have gone undetected. Continuous Holter monitoring would be the only way to get a comprehensive representation of the AF prevalence, but unfortunately this is not feasible in large long term cohort studies such as the Women's Health Study. Third, defining the initial AF episode and AF patterns over time accurately may be challenging, especially when approximately 10% of women are asymptomatic at the time of AF diagnosis.

Finally, standardized echocardiograms were not performed in the Women's Health Study, and thus, we relied on information from echocardiograms provided in the medical records. This likely introduced greater variability and error in the measurement of LA size, which

would probably bias our results toward the null. Furthermore, LA volume seems to be a more robust predictor of cardiovascular events compared with LA diameter (25), but information on LA volume was unavailable in this study. Therefore, reliance on anteroposterior LA diameter as measure of LA enlargement might have introduced some misclassification bias. In addition, while the majority of echocardiograms were performed close to the AF diagnosis, a small minority were performed several months after AF diagnosis. This combined with possible delayed AF diagnosis in asymptomatic patients likely led to some degree of secondary AF-related LA enlargement in our data. Indeed, we found a slightly higher proportion of women with AF and LA enlargement to be asymptomatic or to have had a significant delay between AF diagnosis and time of echocardiogram. However, our results were similar when we adjusted for time between AF diagnosis and echocardiography and symptom status in the case-only regression analysis, and none of the clinical covariates were significantly associated with a delay in echocardiography. Finally, we were unable to assess the relationship between LA size and new-onset AF, because echo measures were lacking in women who did not develop AF.

Conclusions

In this prospective study, we found that age and body weight had stronger risk estimates for incident AF with LA enlargement compared to AF without LA enlargement. On the other hand, age, height, hypertension and exercise were significantly associated with AF in the context of normal LA size, providing evidence that these risk factors may have an effect on incident AF that is independent of LA enlargement. The fact that the relative risk estimates for height and hypertension did not depend on LA size underscores the importance of these pathways. By contrast, the strong relationship between body weight and AF was only present in incident AF with LA enlargement, suggesting that LA remodeling is a major prerequisite for the association between obesity and AF occurrence. The biological underpinnings of these differential relationships remain to be determined in future studies.

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Table 1

Baseline characteristics among women with incident AF, stratified by available information on LA size

Characteristic (N=1072)	AF with information on LA size (N=796)	AF with missing information on LA size (N=276)	P value*
Age, years	58 (52–65)	59 (53–65)	0.50
Height, m	1.65 (1.63–1.70)	1.65 (1.63–1.70)	0.25
Body weight, kg	73 (63–84)	73 (64–85)	0.22
Body mass index, kg/m^2 ‡	26.1 (23.2–30.6)	26.6 (23.7–30.4)	0.49
Hypertension, %			0.14
Yes	325 (40.9)	127 (46.0)	
No	470 (59.1)	149 (54.0)	
Diabetes, %			0.58
Yes	34 (4.3)	14 (5.1)	
No	762 (95.7)	262 (94.9)	
Hypercholesterolemia, %			0.44
Yes	274 (34.4)	88 (31.9)	
No	522 (65.6)	188 (68.1)	
Smoking, %			0.30
Current/Past	400 (50.4)	149 (54.0)	
Never	394 (49.6)	127 (46.0)	
≥2 alcoholic drinks / day, %	39 (4.9)	17 (6.2)	0.42
Physical activity, %			0.65
Rarely/Never	359 (45.2)	119 (43.1)	
< 1x/week	145 (18.2)	48 (17.4)	
1-3x/week	209 (26.3)	73 (26.5)	
≥ 4/week	82 (10.3)	36 (13.0)	
Race/ethnicity, %			0.40
White	770 (97.7)	272 (98.6)	
Other	18 (2.3)	4 (1.5)	

AF=Atrial fibrillation; LA=Left atrial. Data are medians (interquartile range) or counts (percentages). Number of observations across categories may not sum to the given numbers because of missing data.

*P value comparing women with incident AF with versus without LA enlargement. Continuous and categorical variables were compared using Kruskal-Wallis tests and chi-square tests, respectively.

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Table 2

Baseline characteristics according to LA size

	All participants (N=34713)	AF without LA enlargement (N=468)	AF with LA enlargement (N=328)	P value*
Age, years	53 (49–59)	58 (52–64)	60 (54–65)	0.003
Height, m	1.65 (1.60–1.68)	1.65 (1.60–1.70)	1.65 (1.63–1.70)	0.04
Body weight, kg	68 (60–77)	69 (61–82)	75 (66–90)	<0.0001
Body mass index, kg/m^2 ‡	24.9 (22.5–28.3)	25.6 (22.8–29.2)	27.4 (24.2–32.1)	<0.0001
Hypertension, %				<0.0001
Yes	8759 (25.2)	163 (34.9)	162 (50.6)	
No	25947 (74.8)	304 (65.1)	166 (49.4)	
Diabetes, %				0.01
Yes	845 (2.4)	13 (2.8)	21 (6.4)	
No	33851 (97.6)	455 (97.2)	307 (93.6)	
Hypercholesterolemia, %				0.17
Yes	10106 (29.1)	152 (32.5)	122 (37.2)	
No	24593 (70.9)	316 (67.5)	206 (62.8)	
Smoking, %				0.54
Current/Past	16783 (48.4)	231 (49.5)	169 (51.7)	
Never	17904 (51.6)	236 (50.5)	158 (48.3)	
≥2 alcoholic drinks / day, %	1359 (3.9)	19 (4.1)	20 (6.1)	0.19
Physical activity, %				0.64
Rarely/Never	13088 (37.7)	209 (44.7)	150 (45.9)	
< 1x/week	6880 (19.8)	90 (19.2)	55 (16.8)	
1-3x/week	10960 (31.6)	125 (26.7)	84 (25.7)	
≥ 4/week	3770 (10.9)	44 (9.4)	38 (11.6)	
Race/ethnicity, %				0.10
White	32736 (95.1)	450 (97.0)	320 (98.8)	
Other	1678 (4.9)	14 (3.0)	4 (1.2)	
Paroxysmal AF	-	346 (73.9)	149 (45.4)	<0.0001
Echocardiography >1 month after AF onset	-	41 (8.8)	52 (15.9)	0.002

AF=Atrial fibrillation; LA=Left atrial. Data are medians (interquartile range) or counts (percentages). Number of observations across categories may not sum to the given numbers because of missing data.

* P value comparing women with incident AF with versus without LA enlargement. Continuous and categorical variables were compared using Kruskal-Wallis tests and chi-square tests, respectively.

Table 3

Risk factors for AF with and without LA enlargement

Risk factor	AF without LA enlargement (N=468)	P value	AF with LA enlargement (N=328)	P value	P value*
Age, per year					<0.0001
Age-adjusted	1.08 (1.06–1.09)	<0.0001	1.10 (1.09–1.12)	<0.0001	
Multivariable adjusted†	1.08 (1.06–1.09)	<0.0001	1.12 (1.10–1.14)	<0.0001	
Height, per 10 cm					0.66
Age-adjusted	1.42 (1.23–1.64)	<0.0001	1.77 (1.49–2.10)	<0.0001	
Multivariable adjusted†	1.29 (1.10–1.50)	0.001	1.36 (1.13–1.63)	0.001	
Body weight, per 10 kg					<0.0001
Age-adjusted	1.15 (1.08–1.22)	<0.0001	1.46 (1.38–1.55)	<0.0001	
Multivariable adjusted†	1.07 (0.998–1.14)	0.06	1.34 (1.26–1.43)	<0.0001	
Hypertension					0.17
Age-adjusted	1.63 (1.34–1.99)	<0.0001	2.64 (2.02–3.46)	<0.0001	
Multivariable adjusted†	1.55 (1.25–1.92)	<0.0001	1.99 (1.49–2.65)	<0.0001	
Diabetes					0.46
Age-adjusted	1.21 (0.87–1.67)	0.26	2.21 (1.63–3.00)	<0.0001	
Multivariable adjusted†	1.02 (0.73–1.44)	0.90	1.22 (0.87–1.72)	0.24	
White race					0.12
Age-adjusted	1.53 (0.90–2.61)	0.12	3.66 (1.36–9.80)	0.01	
Multivariable adjusted†	1.49 (0.87–2.54)	0.15	3.42 (1.27–9.20)	0.01	
Alcohol ≥2 drinks/day					0.31
Age-adjusted	1.16 (0.77–1.75)	0.48	1.32 (0.83–2.10)	0.24	
Multivariable†	1.10 (0.71–1.69)	0.68	1.54 (0.95–2.49)	0.08	
Current/Past smoking					0.64
Age-adjusted	1.02 (0.85–1.22)	0.84	1.13 (0.91–1.40)	0.28	
Multivariable adjusted†	1.00 (0.83–1.20)	0.98	1.07 (0.85–1.34)	0.56	
Exercise‡					0.20
Age-adjusted	0.88 (0.81–0.96)	0.005	0.91 (0.82–1.01)	0.06	
Multivariable adjusted†	0.90 (0.82–0.98)	0.02	0.98 (0.88–1.10)	0.76	

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AF=Atrial fibrillation, LA=Left atrial

*P values from likelihood ratio tests of the null hypothesis that a risk factor has a uniform effect on AF with versus without enlargement, versus the alternative of different effects; based on the multivariable model assuming different effect for all other risk factors.

†Multivariable models were adjusted for age, height, body weight, hypertension, diabetes, race, education, alcohol consumption, smoking and exercise, using time-varying covariates. Multivariable models were based on 762 AF events in 33354 women.

‡Exercise was entered in the multivariable models as an ordinal variable representing categories described in Table 1

Table 4

Differential associations for incident AF with and without LA enlargement using case-only logistic regression analysis

Risk factor	AF without LA enlargement (N=468)	AF with LA enlargement (N=328)
Age, per year		
Model 1 *	1.0 (Reference)	1.05 (1.03–1.07)
Model 2 †	1.0 (Reference)	1.04 (1.02–1.06)
Height, per 10 cm		
Model 1 *	1.0 (Reference)	0.96 (0.74–1.25)
Model 2 †	1.0 (R 2.0 eference)	0.96 (0.72–1.27)
Body weight, per 10 kg		
Model 1 *	1.0 (Reference)	1.33 (1.20–1.48)
Model 2 †	1.0 (Reference)	1.33 (1.19–1.48)
Hypertension		
Model 1 *	1.0 (Reference)	1.26 (0.88–1.81)
Model 2 †	1.0 (Reference)	1.21 (0.82–1.78)
White race		
Model 1 *	1.0 (Reference)	2.04 (0.63–6.61)
Model 2 †	1.0 (Reference)	2.94 (0.76–11.34)
Exercise ‡		
Model 1 *	1.0 (Reference)	1.11 (0.97–1.29)
Model 2 †	1.0 (Reference)	1.15 (0.99–1.34)
Asymptomatic AF		
Model 1 *	-	-
Model 2 †	1.0 (Reference)	1.57 (0.95–2.60)
Paroxysmal AF		
Model 1 *	-	-
Model 2 †	1.0 (Reference)	0.31 (0.22–0.44)
Echo >6 months after AF onset		

Risk factor	AF without LA enlargement (N=468)	AF with LA enlargement (N=328)
Model 1 *	-	-
Model 2 †	1.0 (Reference)	2.41 (1.59–3.66)

Data are Odds ratios (95% confidence intervals)

*Model 1 adjusted for age, height, body weight, hypertension, diabetes, race, education, alcohol consumption, smoking and exercise

†Model 2 additionally adjusted for symptom status at AF onset, AF pattern (paroxysmal versus non-paroxysmal) and time between AF diagnosis and echocardiography

‡Exercise was entered in the multivariable models as an ordinal variable representing categories described in Table 1